# PATENT COOPERATION TREATY

# PCT

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



| Applicant's or agent's file reference LRD-PCT-413 | **FOR FURTHER ACTION** | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/BE 03/00172 | International filing date *(day/month/year)* 10.10.2003 | Priority date *(day/month/year)* 10.10.2002 |
| International Patent Classification (IPC) or both national classification and IPC C12Q1/68 | | |
| Applicant K.U. LEUVEN RESEARCH AND DEVELOPMENT et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☐ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 29.04.2004 | 21.01.2005 |
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized Officer Schmitt, C Telephone No. +49 89 2399-7351 |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.: PCT/BE 03/00172

## I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

**Description, Pages**

1-53 as originally filed

**Claims, Numbers**

1-62 received on 09.12.2004 with letter of 09.12.2004

**Drawings, Figures**

1-4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☒ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   *(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

   **see separate sheet**

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☒ the entire international application,

   ☐ claims Nos.

   because:

   ☒ the said international application, or the said claims Nos. 1-18, 44-48 relate to the following subject matter which does not require an international preliminary examination (specify):

   **see separate sheet**

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-48, 50-57, 61, 62 are so unclear that no meaningful opinion could be formed *(specify)*:

   **see separate sheet**

   ☒ the claims, or said claims Nos. 1-48, 50-57, 61, 62 are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 49, 58-60

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

The applicant's arguments provided with the letter dated 9.12.2004 have been taken into consideration to established the present IPER.

**Amendments**

Amended claim 2, which is dependent on independent claim 1, filed with the letter dated 9.12.2004 relates to a method for testing or screening an animal thought to have or to be predisposed to have a neural system disorder comprising detecting a specific type of modification of the NBEA gene or its promoter which causes a loss of biological function of the NBEA gene product.
No basis for such an amended claim 2 has been given by the applicant and the only passages found by the International Examination Authority is claim 2 as originally filed which relates to such a method wherein, in addition to the step of detecting a modification in the NBEA gene or its promoter, a correlation step of the modification/mutation of the NBEA gene with a potential for a neuronal system disorder is performed.
Thus, amended claim 2 introduce subject-matter which extends beyond the content of the application as originally filed. The present report is therefore established as if said amendment had not been made (Rule 70.2 (c) PCT).
The same applies to claims depending directly or indirectly on amended claim 2 (i.e. claims 4-6 and 10-18).
In the following amended claim 2 will be examined as if it is relating to the subject-matter of originally filed claim 2 or amended claim 3 (i.e. step of detection of a modification and step of correlation of the mutation detected with a potential for a neural system disorder).

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Reference is made to the following documents:

D1: Smith et al., "Molecular genetic delineation of a deletion of chromosome 13q12-q13 in a patient with autism and auditory processing deficits.",
Cytogenetic and Genome Research (2002), 98(4), 233-239.
*Document D1 was available to the public on June 2003.*

D2: Wang et al., "Neurobeachin: a protein kinase A-anchoring, beige/Chediak-higashi protein homolog implicated in neuronal membrane traffic."
The Journal of Neuroscience: The official Journal of the Society for Neuroscience, December 2000, 20(23), 8551-8565.

D3: Steele et al., "Brief report: a case of autism with interstitial deletion of chromosome 13."
Journal of Autism and Developmental Disorders, April 2001, 31(2), 231-234.

D4: Bradford et al., "Incorporating language phenotypes strengthens evidence of linkage to autism."
American Journal of Medical Genetics, 08-08-2001, 105(6), 539-547.

D5: US 6228582, published 08.05.2001.

1. Claims 49 and 58-60 were not searched (see International Search Report). Said claims are therefore not further examined.

2. Independent claim 1 relates to a method of testing/screening an "animal to have [...] a neural system disorder" comprising detecting the presence of a mutation in the NBEA gene or its associated promoter in a sample of said animal and encompasses, in view of dependent claim 7, a step of "providing biological material from said animal" and amounts thus a step of surgery practised on the human or animal body. Claim 1 and claims depending thereon (i.e. claims 2-18) relate, therefore, to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).
It is to be pointed out that said objection would have been overcome by deleting such a step of "providing biological material from the animal" from claim 7 and by deleting any equivalent statement(s) from the description.

Similarly, claims 44-47 and claim 48 relate to a method of screening for a therapeutic agent that encompass a step of surgery practised on the human or animal body (i.e. the step of "providing a cell" in independent claim 44, wherein the term "cell" is considered as encompassing the human or animal body or the step of "introducing to the animal a agent to be screened" in independent claim 48). Claims 44-48 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion

will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

3. Furthermore, no opinion on novelty and inventive step can be given for claims 1-48, 50-57, 61 and 62 due to lack of clarity, support and/or disclosure of said claims (Articles 5 and 6 PCT).

3.1. The present application fails to provide any information on the DNA/protein sequence that encodes/comprises NBEA variants/mutants. It has thus been considered that claim 33, relating to a polynucleotide sequence comprising at least one mutation of the NBEA gene that causes a loss of biological function in the NBEA gene was unclear in the sense of Article 6 PCT.
The applicant's arguments were not considered to be convincing and the lack of clarity of claim 33 is thus maintained. In particular, the polynucleotide of claim 33 is defined as comprising at least one mutation in the NBEA gene that causes a loss of biological function in the NBEA gene. Such a functional feature are only permissible in a claim, if from an objective viewpoint, such features cannot otherwise be defined more precisely without restricting the scope of the claim, and if this feature provide instructions which are sufficiently clear for the expert to reduce them to practice without undue burden, if necessary with reasonable experiments.
The present description (page 5, lines 10-14) provide the skilled person with the information that aberrant NBEA gene expression can be assessed or that the function of the NBEA gene can be assessed by measuring either the enzyme activity of the protein or its binding capacities to any substrate, of any kind. The instructions that enzymatic activity or binding activity can be assessed is however not considered to be sufficiently clear and precise so as to allow the skilled person to reduce them to practice without undue burden as no indications of any kind are given as to which enzymatic activity is to be tested or as to which binding to which substrate is to be tested to assess the loss of biological function of the NBEA gene.
Thus, in the present case, the functional feature defining the mutation as causing a "loss of biological function" of the NBEA gene is not considered to be sufficiently clear and precise so as to allow the skilled person to clearly and unambiguously understand the scope of the claim (Article 6 PCT).

Thus, claims relating to NBEA nucleic acids (i.e. claim 33), claims relating to the use of such nucleic acids (i.e. claims 19-26) or proteins (i.e. claims 27-32), claims relating to products

derived from the NBEA nucleic acids (i.e. claims 34-43) and claims relating to methods for screening therapeutic agents based on such NBEA nucleic acid (i.e. claims 44-48 and 51) are unclear in the sense of Article 6 PCT.
Similarly, claims 19 and 20 which relate to the use of a polynucleotide sequence, wherein said polynucleotide sequence is only defined in terms of its function namely that it is hybridisable with a variant NBEA gene, are also unclear in the sense of Article 6 PCT.

3.2. The present application relates, in particular, to methods for testing/screening for mutation(s) in the NBEA gene that are linked to a neural system disorder (i.e. claims 1-18).
As indicated in the applicant's reply, once a mutation has been identified, linkage to a disease can be confirm by segregation analysis.
However, even if it is well known that once a mutation has been identified, linkage to a particular phenotype can be assessed, the skilled person will have to assess every single mutation for its possible association with a certain phenotype (i.e. in the present case, neural disorders) and this cannot be performed without undue burden, in particular as, most of the mutation(s) occurring across the genome are not linked to any phenotype.
The skilled person would not be able without undue burden to identify or assess mutations in the NBEA gene for their possible association with neural disorder, such as autism.

Furthermore, the applicant has identified a breakpoint on 13q12 in a single autistic patient resulting in the disruption of the neurobeachin gene (example 1). However the applicant does not provide any data showing that said breakpoint causes aberrant NBEA gene expression or expression of an aberrant NBEA gene product nor does he provide any statistical analysis of the incidence of a particular allele in two groups of individuals with and without autism showing that said gene is indeed linked to the autistic phenotype. Therefore, the fact that a translocation on 13q12 is present in a single autistic patient is not sufficient to "demonstrate" that the NBEA gene is indeed linked to autism, even when the genetic basis of such disease is polygenic.
In addition, no data are provided in the present application as to any mutation in the NBEA gene as being linked to any other neural disorder.

Thus, claim 1 and claims depending thereon (i.e. claims 2-18) cover subject-matter not sufficiently disclosed in the sense of Article 5 PCT, and therefore are, in addition, not supported by the description within the meaning of Article 6 PCT.

**3.3.** In view of the above objections and in the absence of any clearly defined mutation in the NBEA gene which is linked to autism, serious doubts as regards the possibility of carrying out the methods of independent claims 1, 44, 48, 52 and 61 and claims depending thereon (i.e. 2-18, 45-47, 53-55, 57, 62) exist.

**4.** The application as a whole thus does not meet the requirements of Articles 5 or/and 6 PCT and no opinion on novelty, inventive step and industrial applicability can be given for claims 1-48, 50-57, 61 and 62.